EXHIBIT 1

2 OF 3

REDACTED

149. I am not the only scientist to object to this methodology. Bayer's method of averaging in zeroes was also criticized by FDA. In a letter to Bayer (then Berlex), dated 2 June 1998, FDA reviewed the label for a COC product now called *Levlite*®, and specifically objected to the inclusion of zeroes. The FDA official wrote "Figure for EE concentrations (in Figure 1) should be removed or altered so that concentration points below the lower limit of quantitation for the assay are not included." The sponsor apparently argued that adding to the label the fact that zeroes were averaged in was an adequate response to this point, and the *Levlite*® label since 1998 includes:

> In calculating the mean concentration for ethinyl estradiol, any individual subject value below the quantifiable limit (i.e., 20 pg/mL) was converted to 0; and the 0 values were included for calculation of the mean concentration.

Such a statement does not appear in the *Yasmin*® or *Yaz*® labels. Perhaps the FDA examiners did not explore the Appendices of the various DRSP studies closely enough to realize that zeroes were being averaged in. FDA also noted concern about the assays themselves in the same 2 June 1998 letter, stating that the methods "were less than desirable," as "more sensitive assays can be used for the determination of EE2 and LNG in serum."

150. I am at a loss to understand why Bayer staff would have adopted this inaccurate method (averaging in zeroes) in the first place, and why they continued with it, and why they did not state it in their COC labels (except in the case above, when required by FDA). Clearly Bayer's technique gives systematically lower values of AUC for contraceptive steroids such as ethinyl estradiol, and the less sensitive the assay (*i.e.*, the higher the LLOQ), the lower the value for this key pharmacokinetic ("PK") parameter. Recall that the AUC for a drug reflects total exposure to that drug.

151. I am unable to find a scientific justification for averaging in zeroes. Looking back through papers describing the radioimmunoassay the organization was using for measurements of contraceptive steroid concentrations, I found an older review article (Kuhnz *et al.*, *Drug Res.* 43: 16-21, 1993) on EE radioimmunoassay methods by Bayer (then Schering) staff that explained but failed to justify the methodology. The following appears on the last page of the paper.

> "The contribution of a variable blank is of course most crucial in the sample ... where EE_2 concentrations are close to the limit of quantitation. Our common practice is to determine a lower limit of quantitation and to set all values below that limit to zero. If the individually measured blank value is above the quantitation limit, the actually determined concentration value is used for further calculations, like AUC. This is a somewhat arbitrary procedure. ... It

would of course be equally justified to set these values equal to the limit of quantitation instead of zero."

152. I agree with Kuhnz *et al.* (1993) that averaging in zeroes "is a somewhat arbitrary procedure". It is my opinion that Bayer's "common practice" is scientifically invalid and gives systematically low values for concentrations "used for further calculations, like AUC." It would lead to drug labels stating AUC values lower than AUCs calculated properly.

XVIII. AUCs from COC labels

153. Since AUC (total drug exposure) is calculated from concentrations at various time points, systematically lower concentrations lead to systematically lower AUCs. For $AUC_{0\text{-}24h}$ for EE on Day 21 of Cycle 1, Bayer reports in AI98 and in the *Yasmin*® label, a value of 461 ± 433 pg-h/ml, or 461 pg-h/ml (CV=94%). Two things struck me about this AUC for EE from Bayer Study AI98.

154. The first was that 461 pg-hr/ml was very low for this parameter (EE $AUC_{0\text{-}24h}$) vs. other COCs containing 30 µg/d EE. The second was that the variability (as expressed by sd or %CV) was very high vs. that of other COCs. From labels (accessed at fda.gov or drugs.com) and from the scientific literature (Kuhnz *et al.*, *Contraception* 46: 455-469, 1992; Sidhu *et al.*, *Brit. J. Clin. Pharmacol.* 61: 191-199, 2005; Muirhead *et al.*, *Brit. J. Pharmacol.* 49Suppl1: 45S-49S, 2000; Ragueneau-Majlessi *et al.*, *Epilepsia* 43: 697-702, 2002), I found 13 values for EE $AUC_{0\text{-}24h}$ for contraceptives between containing 30 µg/d EE. The EE $AUC_{0\text{-}24h}$ values for Cycle 1, Day 21 (or a nearby day after steady-state had been reached) for those other 30 µg/d EE COCs ranged from 728 to 1117 pg-hr/ml. The average of these values was 932 (N=10, after some duplicates removed), with an average %CV of 27% (N=7, not all sd were reported). The EE AUC_{24} from the *Yasmin*® label was the lowest of all the EE AUC_{24} values I could find. The EE AUC_{24} values for six commercial products are compared in the figure below with the corresponding value from the *Yasmin*® label and from the Bayer A470 study (discussed in detail below). Clearly the *Yasmin*® label (red) is the outlier. It is an outlier both because its EE AUC_{24} is very low compared with the same parameter for the other 30 µg/d EE COCs, and because it %CV (variability) is very high compared with the same parameter for the other 30 µg/d EE COCs.

155.

Yasmin® label (Bayer Study AI98) EE AUC_{24} is less than other 30 µg/d EE COCs and less than Bayer Study A470

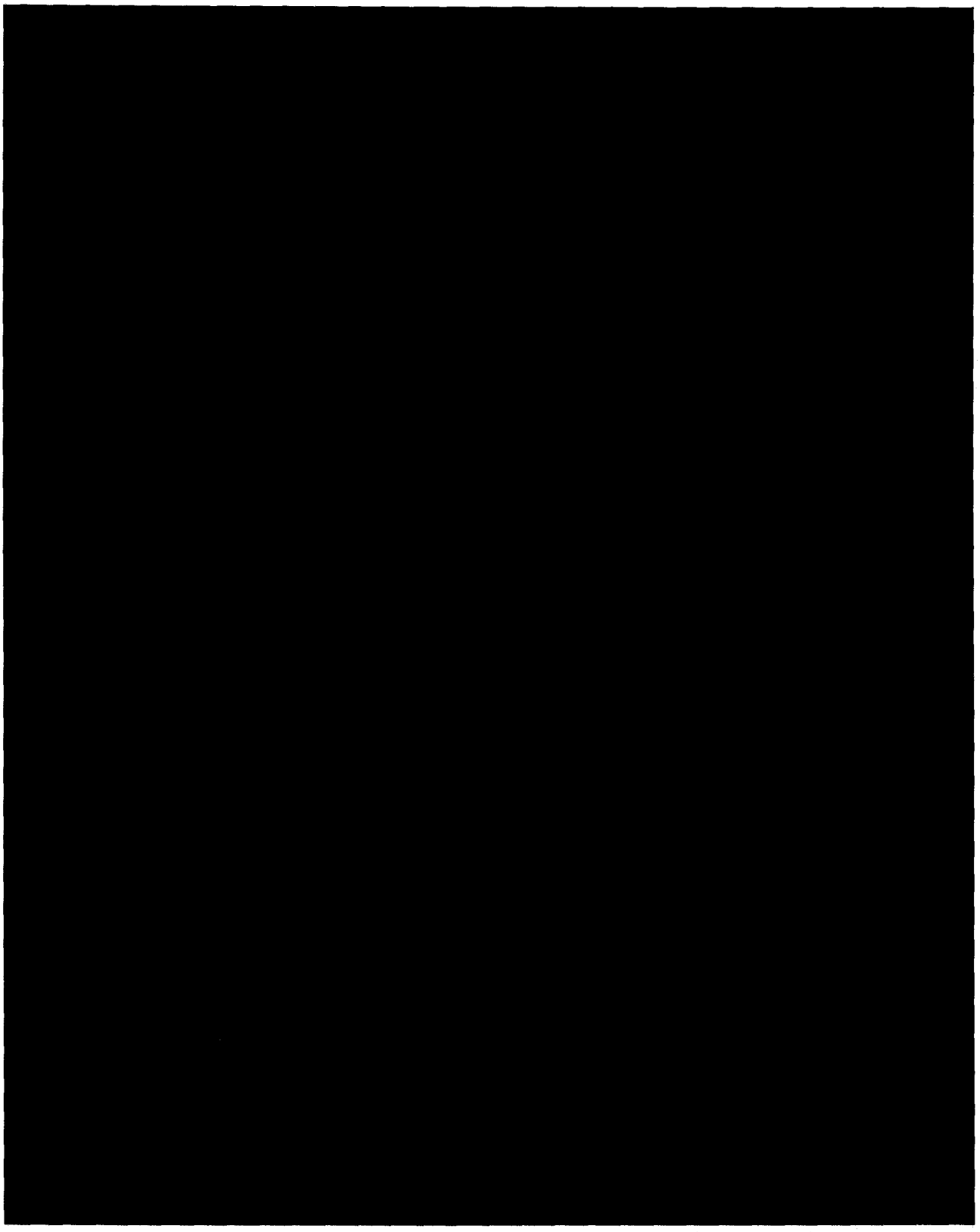
EE AUC_{0-24h} in some 30 µg/d EE COCs[1]

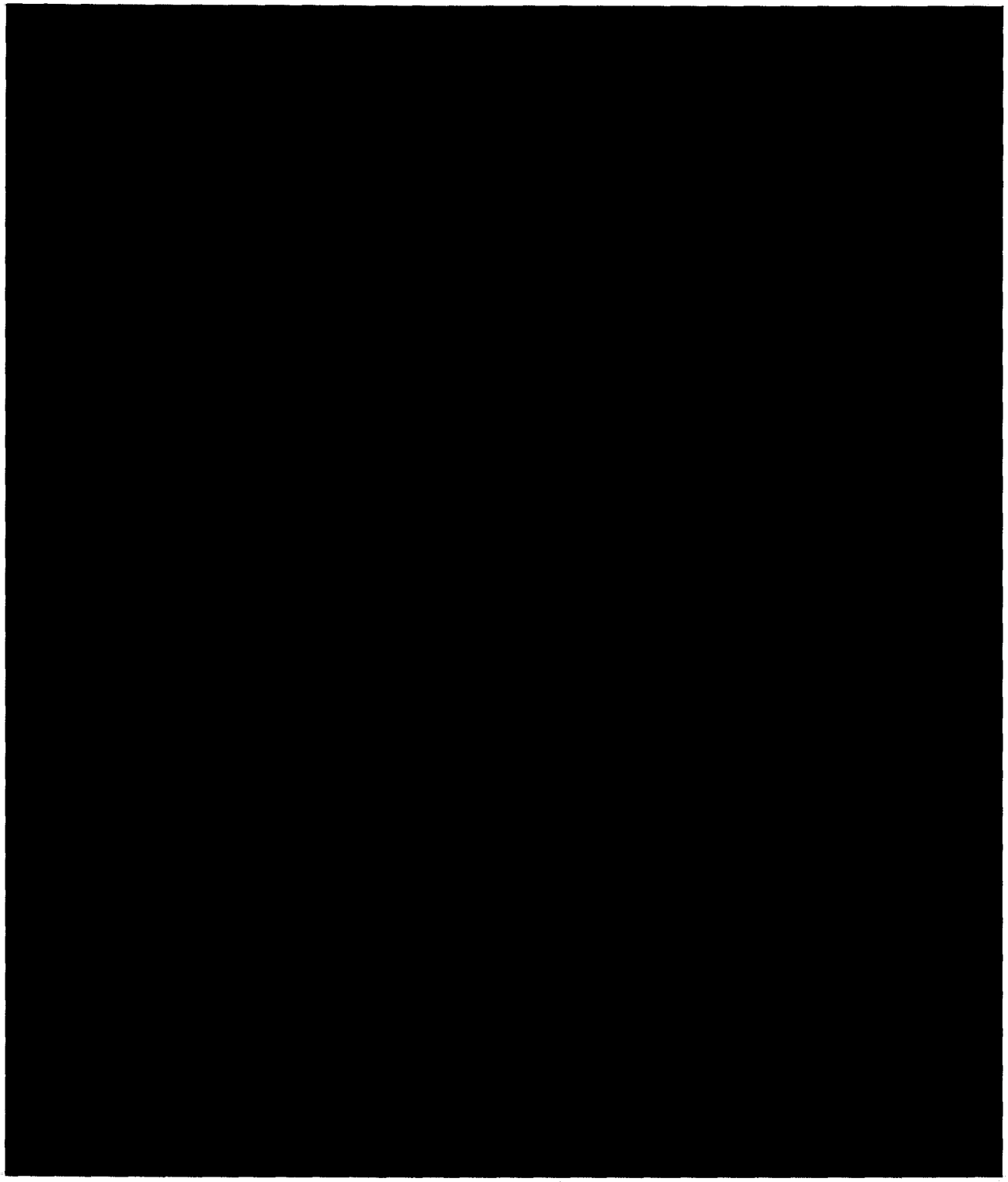
Apri®	**1117±34%**	***Estrostep*** ®	**973±30%**
Microgynon®	**778±41%**	***Microgynon***®	**785±34%**
Ovranette®	**794±28%**	***Trivora***®	**1072±16%**
Average of six products above			**929±31%**
Bayer Study AI98 & *Yasmin*® label			**461±94%**
Bayer Study A470			**1175±52%**

[1] AUCs from drugs.com; fda.gov; Kuhnz *et al.*, *Contraception* 46: 455-469, 1992; Sidhu *et al.*, *J. Clin. Pharmacol.* 61: 191-199, 2006

156. Thus there was good reason for Dr. Loock to write that the EE levels in AI98 were "remarkably low" (Blode deposition of 3 May 2011 at page 137). In fact, the Bayer Study AI98 EE AUC_{24} values, which are the ones on the *Yasmin*® label, are lower than this same parameter from several COCs containing less than 30 µg/d EE. The following COCs containing 20 µg/d EE have AUC_{24} values higher than the *Yasmin*® (30 µg/d EE) label: *Mircette*® (597±127), *Lybrel*® (717±351), *Levlite*® (596±494), *Loestrin 24 FE*®(701±196), *Estrostep FE*® (661±190), *Alesse*® (776±308), all in pg-hr/ml. [Even the 10 µg/d EE COC *Lo LoEstrin FE*® has a higher EE AUC_{24} (621±254) than that indicated for *Yasmin*® on its label.] Given that AUC_{24} is first order with respect to EE dose (well-established; Blode deposition of 3 May 2011 at page 52), the finding that *Yasmin*® (30 µg/d EE) has a lower EE AUC_{24} than several COCs containing ≤20 µg/d EE is very difficult to explain. One potential explanation would be that *Yasmin*® has lower EE bioavailability than the other products. Another potential explanation, and the explanation I consider most likely, would be that the *Yasmin*® label gives an EE AUC_{24} lower than the real value of that parameter.

[redacted]





167. I wondered whether part of the explanation for the low mean value for EE AUC_{24} and/or the high variability in Bayer Study AI98 might be explained by some interference with the EE radioimmunoassay by drospirenone or a metabolite of drospirenone. In the article I

have discussed above (Kuhnz *et al.*, 1993, *op. cit.*), the authors clearly considered the possibility that the co-administered progestin (here gestodene or desogestrel) could affect the measurement of EE, and did experiments to test that. Further, other groups (Orme *et al.*, *Contraception* 43: 305-316, 1991; Jung-Hoffmann & Kuhl, *Contraception* 40: 299-312, 1989) had worried about such an interaction. When I looked in the documents available to me for some study showing that DRSP (or a DRSP metabolite) does or does not cross-react in the EE assay (RIA), I was unable to locate such a measurement. Consistent with my conclusion that such a study was never done is the testimony of Dr. Blode of Bayer, in his deposition of 3 May 2011 at page 19-28. The EE RIA which was used in several Bayer studies to measure EE in the presence of DRSP should have been tested in the presence of DRSP to determine whether the EE measurements were or were not valid in the presence of this progestin. But no such validation studies were ever conducted. This is an important and obvious omission.

[redacted]

169. When selected results of AI98 were published (Blode *et al.*, *Eur. J. Contracept. Reproduct. Health* 5: 256-264, 2000), the fact that EE values <LLOQ were set to zero and the zeroes averaged with real values was not mentioned. I am skeptical that the manuscript would have survived peer review if this point had been included. Manipulation of data of this sort is arbitrary (as stated by Bayer staff, see ¶ 151 above) and, in my opinion, unacceptable. Values below the measuring range of an assay should be left out of calculations; one cannot assume, as Dr. Blode and his colleagues did, that no drug was present in patients whose values were below the sensitivity of the drug assays in use.

170. There are several reasons why, after reviewing Bayer Studies AI98 and A470, I consider the latter more reliable than the former for determination of the pharmacokinetic parameters for EE in the medication that would later be named *Yasmin*®. First, the PK parameters (*e.g.*, EE $AUC_{0\text{-}24h}$) for Study A470 are similar to those for other COCs containing 30 µg/d EE, while those for AI98 are not (see Figure 155 above); instead the values from AI98 are "remarkably low". Second, Study A470 shows a lower variation (CV=52%) from patient to patient than Study AI98 (CV=94%). Third, the Study A470 %CV is in line with studies of other COCs, while the Study AI98 %CV is a good deal larger than that seen with other COCs. Fourth, the A470 study had a significantly larger number of subjects (27 completed) than AI98 (11 completed), and so is more likely to reflect the population who would eventually use the drug. But when faced with a choice about which Study (AI98 or A470) to include in the label, and which study to publish, Dr. Blode (3 May 2011 deposition at page 160-165) chose AI98 for publication and for the label. The EE AUC data from Bayer Study A470 were never published (Blode deposition of 3 May 2011 at page 165-166).

171. As issues concerning the rate of VTEs associated with use of *Yasmin*® began to arise, soon after the product was introduced in the United States, the impact that the "remarkably low" EE levels quoted in the *Yasmin*® label may have had upon FDA's analysts must be considered. With other contraceptive products (*e.g.*, the contraceptive patch *Ortho Evra*®), a concern over high serum levels of EE prompted a label change even before epidemiology studies indicating an increased risk of VTE were published. With *Yasmin*®, although Bayer did provide the information from all studies during initial labeling submissions, the question remains whether the decision to include only the "remarkably low" EE serum levels on the label created a false sense of comfort among FDA medical officers responsible for reviewing ongoing safety information concerning *Yasmin*®.

172. A prescribing physician needs to rely on the EE AUC_{24} values reported in a COC label. It is my opinion that the *Yasmin*® label values for EE AUC_{24} would mislead prescribing physicians into believing that this COC delivers less EE than other COCs containing 30 μg/d EE. They would consider such a low EE exposure attractive from the safety standpoint. They would be less likely to prescribe *Yasmin*® if the label featured EE AUC_{24} values from Bayer Study A470 or EE AUC_{24} values comparable to those of other 30 μg/d EE COCs. If the *Yasmin*® label EE AUC_{24} values were similar to those of other 30 μg/d EE COCs, prescribers would be less likely to prefer *Yasmin*® over other 30 μg/d EE products.

173. A prescribing physician needs to rely on the EE AUC_{24} values reported in a COC label. It is my opinion that the *Yaz*® label values for EE AUC_{24} would mislead prescribing physicians into believing that this COC delivers less EE than other COCs containing 20 μg/d EE. They would consider such a low EE exposure attractive from the safety standpoint. They would be less likely to prescribe *Yaz*® if the label featured EE AUC_{24} values from Bayer Study A49202 or Bayer Study A40196, or values comparable to those of other 20 μg/d EE COCs. If the *Yaz*® label EE AUC_{24} values were similar to those of other 20 μg/d EE COCs, prescribers would be less likely to prefer *Yaz*® over other 20 μg/d EE products.

174. Thus EE exposure from DRSP-containing COCs appears to be higher than EE exposure from COCs containing other progestins at the same EE dose. Several explanations for this observation may be considered.

175. One possibility is that the bioavailability of EE in the DRSP-containing COCs is higher than in COCs containing other progestins. Formulation of the tablets could affect EE bioavailability. Remarkably, Bayer staff never tested EE bioavailability in the DRSP-containing COCs tested in clinical trials (Blode deposition of 3 May 2011, pages 80-90), and Dr. Blode did not know whether or not the EE used in various COCs from Bayer or other vendors was micronized (*op. cit.*). Another curiosity is that the US label and the European label quote different values for EE bioavailability, 40% for the former and 60% for the latter.

176. There is reason to expect that micronization would affect the bioavailability of contraceptive steroids. In Study A15704, Bayer compared the pharmacokinetics of micronized DRSP vs. sieved DRSP (each given as a 3 mg dose to 14 subjects in a randomized crossover design) and found the two not at all bioequivalent, as shown in the Table below.

TT 1: **Mean[1] pharmacokinetic parameters of DRSP**

Treatment	C_{max} [ng/mL]	t_{max} [h]	$t_{1/2}$ [h]	AUC(0-t_{last}) [ngxh/mL]	AUC [ngxh/mL]
SH T00470R (micronized)	34.1 (19.9%)	1 (1-1.5)	39.5 (22.6%)	485 (18.9%)	526 (17.9%)
SH T00470RA (sieved)	8.55 (33.1%)	2.5 (1.5-6)	41.0 (21.5%)	337 (24.9%)	376 (23.1%)

C_{max} = maximum concentration
t_{max} = time to reach C_{max}
$t_{1/2}$ = terminal half-life
AUC(0-t_{last}) = area under the curve up to the last data point above the lower limit of quantitation
AUC = area under the curve up to infinity

Furthermore, the subjects taking the micronized DRSP reported more side effects than the same subjects when taking the sieved DRSP. For example, more than 10% of the volunteers reported hot flashes and nausea while taking the micronized DRSP, but none of these same volunteers reported these symptoms while taking the sieved DRSP.

The Study A15704 investigators concluded:

Conclusions:

The results clearly demonstrate that the particle size distribution of the drug substance has a high impact on the rate and extent of absorption of DRSP in vivo. Considering the large difference in C_{max} and AUC values between Test and Standard formulation on the one hand and the particle size distributions in these formulations on the other hand, the demonstration of bioequivalence between formulations containing micronized and non-micronized DRSP is highly unlikely.

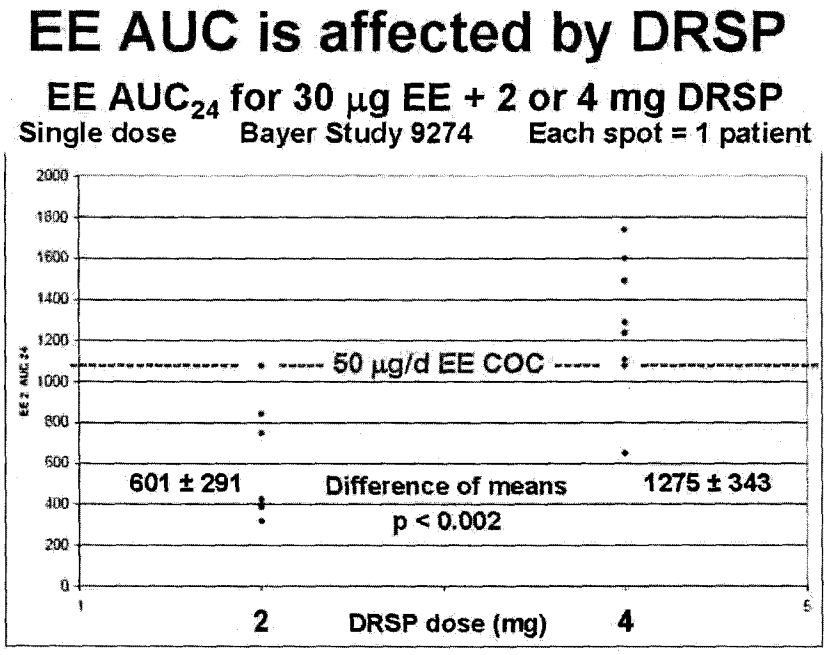
Since the differences between micronized and sieved DRSP in Bayer Study A15704 were significant, both in pharmacokinetics and adverse events, it puzzles me that an investigation of micronized vs. sieved EE was never conducted. Perhaps a higher bioavailability of EE in DRSP-containing COCs may partially explain their higher risk (discussed in Section XIII of this report).

177. Remarkably, Bayer never determined the half-life ($t_{½}$) of EE in DRSP-containing COCs, instead choosing to rely on historical data. While that practice could have been acceptable for a traditional formulation, I do not consider it acceptable for a novel formulation (micronized or clathrated) or with a novel progestin (as in *Yasmin*®, *Yaz*® or another DRSP-containing COC), much less both. While I understand that this measurement would have been difficult using Bayer's insensitive radioimmunoassay for EE, it would certainly have been feasible using GC/MS. [Gas chromatography coupled with mass spectrometry is the "more sensitive" method that FDA recommended to Bayer in its letter of 2 June 1998 (see ¶ 149) when noting that Bayer's RIA method for determining EE concentrations was "less than desirable".] A table of pharmacokinetic parameters in a drug label which does not include a value for the half-life of an active component is very unusual, but that is what one finds in the labels of *Yasmin*® and *Yaz*®. If EE had a longer $t_{½}$ in DRSP-containing COCs than in other COCs, other factors being equal, users of the former products would have a greater EE exposure and a higher EE AUC_{24} than users of the latter products.

178. Another possible explanation for the higher EE levels seen with the *Yasmin*® family of COCs is that DRSP affects EE metabolism. There are several compounds that are known to affect the metabolism of EE by the liver (*e.g.*, Back & Orme, *Clin. Pharmacokinet.* 18: 472-

484, 1990). Although Bayer staff were careful to verify that the presence of EE did not affect DRSP bioavailability or metabolism, they never tested whether DRSP would have any effect on EE bioavailability or metabolism (Blode deposition of 3 May 2011, pages 80-100). However, some data suggesting that EE AUC_{24} is in fact affected by DRSP dose are available in Bayer Study 9274. In this study, 30 µg EE was given to volunteers along with two different doses of DRSP, 2 mg or 4 mg. This single dose study is shown in the figure below. At the higher (4 mg) DRSP dose, EE AUC_{24} was significantly higher than at the lower (2 mg) DRSP dose. My conclusion from these results is that EE bioavailability or metabolism is affected by DRSP, and that it was poor practice not to look into that possibility further.

179.



The groups had 7 (2 mg DRSP) and 8 (4 mg DRSP) volunteers, with the means and standard deviations shown beside each spots column. A dotted line at 1065 pg-hr/ml indicates the single dose EE AUC_{24} for a 50 µg/d EE COC. COCs containing >50 µg/d EE were banned by FDA in 1988. The position of the dotted line was determined by averaging the EE AUC_{24} values for single doses of three commercial products and one experimental formulation each containing 50 µg EE, all of which gave identical results within experimental uncertainty (Back *et al.*, *Contraception* 20: 263-273, 1979; Crawford *et al.*, *Brit. J. Clin. Pharmacol.* 30: 892-896, 1990). The experimental formulation (AUC_{24}=1048±247) contained no progestin, *Minovlar*® (AUC_{24}=948±212) contained 1 mg norethindrone, *Eugynol*® (AUC_{24}=882±436) contained 0.25 mg levonorgestrel, and *Gynlovar*® (AUC_{24}=1200±87) contained 3 mg norethindrone. The difference of the means of the 2 mg and 4 mg DRSP groups was highly statistically significant at $p < 0.002$. None of the 2 mg DRSP group, but more than half of the 4 mg DRSP group, had EE AUC_{24} higher than the mean of a 50 µg/d EE COC.

XIX. Clinical Studies of *Yasmin*® or *Yaz*®

180. What follows is a summary and overview of the some of the clinical pharmacology studies (*i.e.*, human subjects trials) of *Yasmin*® family (drospirenone-containing) COCs. Some

studies were performed during the years leading up to launch as a commercial product, while others were performed after the products were on the market. I will focus primarily on the multiple dose (rather than single dose) studies, since COCs are used chronically.

181. The studies are arranged below in chronological order. At the time some of these studies were performed, the sponsor was noted as "Berlex" or "Schering". Both the latter are now part of Bayer Schering AG, which I refer to as "Bayer". Some studies have both a protocol number and a report number. Medications used in these clinical studies are referred to by designations other than the proprietary names. Thus SH T 470 F (3 mg/d DRSP + 30 µg/d EE) in Bayer Study A470 is essentially the same medication sold under the proprietary name *Yasmin*®.

182. **Bayer Study 9274.** Protocol 89097. "Controlled study on pharmacodynamics and pharmacokinetics of the combination drospirenone / ethinylestradiol over 3 months with Microgynon as a reference." Final Report January 1993. Study dates September 1989 to April 1990. 27 volunteers completed. One group had 2 mg/d DRSP, a second 4 mg/d DRSP, each with 30 µg/d EE; the third group used a commercial COC with 30 µg/d EE. Neither experimental preparation matches the DRSP content of *Yaz*® and *Yasmin*® (3 mg/d DRSP). The pharmacokinetics of DRSP was clearly first order (dose-proportional), reaching steady-state at about 7d. The diuretic activity of DRSP was clear, and dose-dependent, Volunteers taking 4 mg DRSP produced more urine with than those taking 2 mg. The EE PK results were published for *Microgynon*® only, and for multiple dose only (Kuhnz *et al.*, *Contraception* 46: 455-469, 1992).

183. Multiple dose only. EE $AUC_{0\text{-}24h}$ only, all 30 µg/d EE.

Cycle	2 mg DRSP	4 mg DRSP	*Microgynon*® 0.15 mg LNG
1	542 ± 421 (N=9) 542 (%CV=78)	793 ± 266 (N=9) 793 (%CV=34)	729 ± 314 (N=9) 729 (%CV=43)
3	796 ± 579 (N=9) 796 (%CV=73)	1050 ± 408 (N=9) 1050 (%CV=39)	778 ± 318 (N=9) 778 (%CV=41)

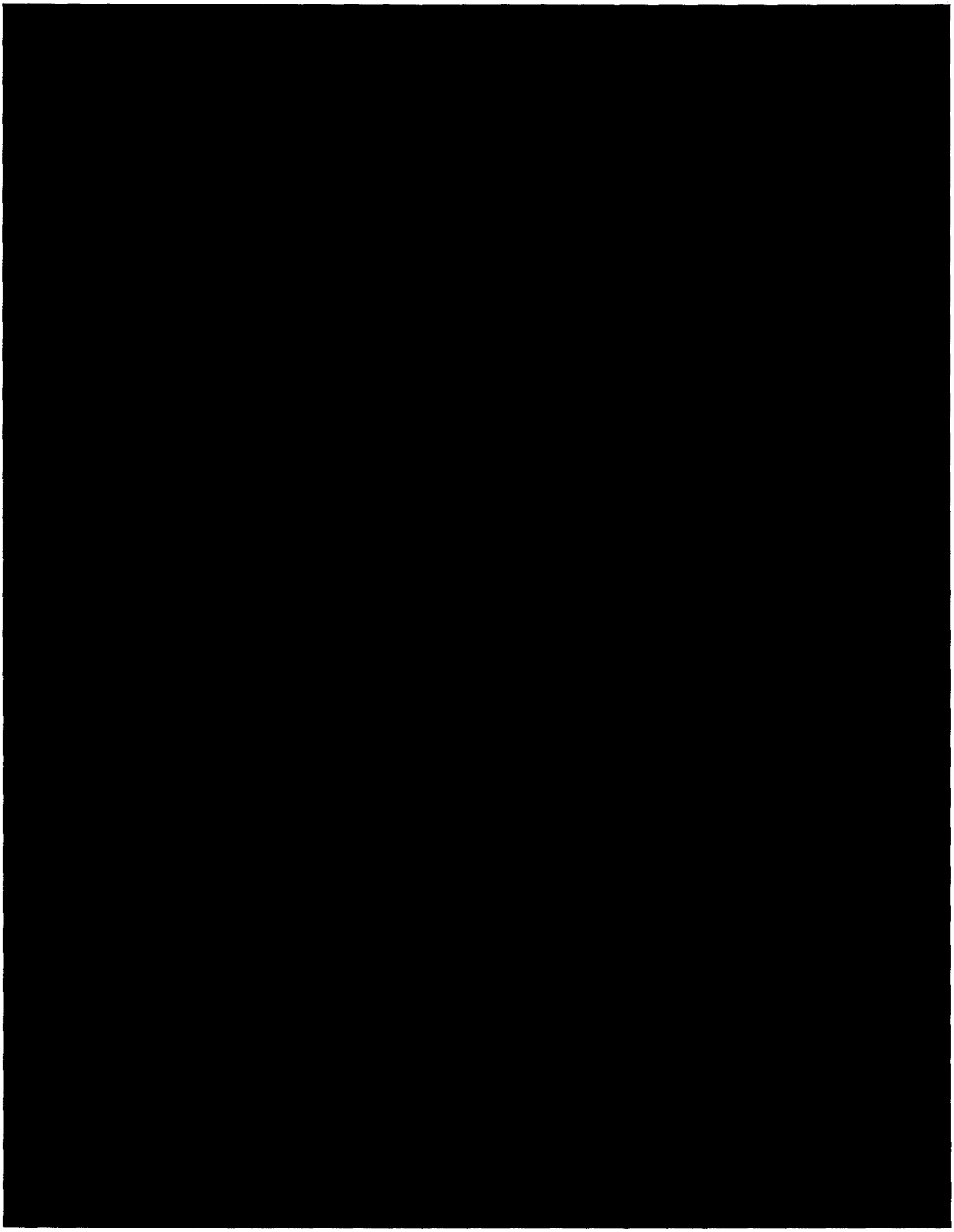
No statistically significant differences here (sample sizes too small).

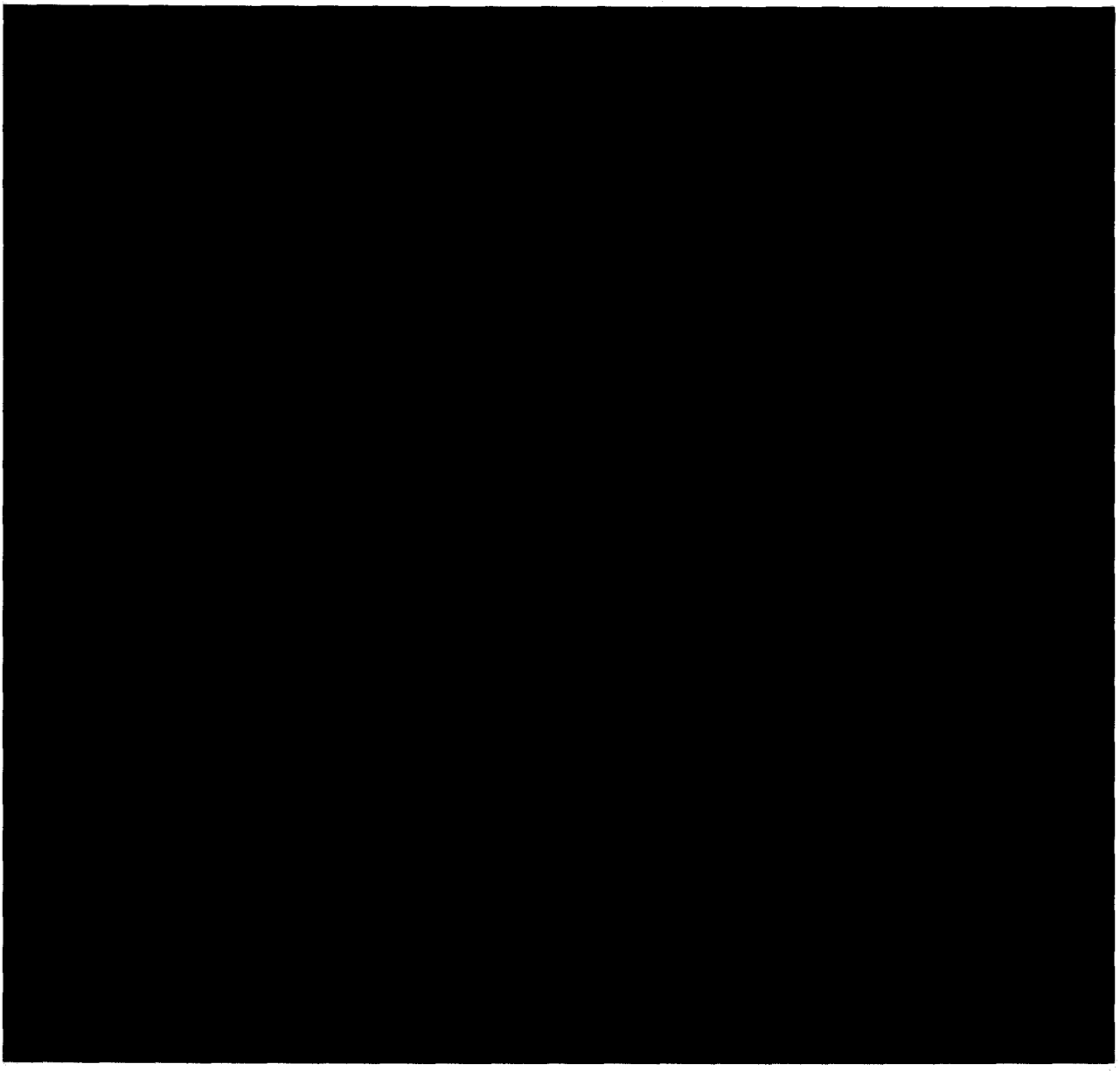
184. Single administration only:

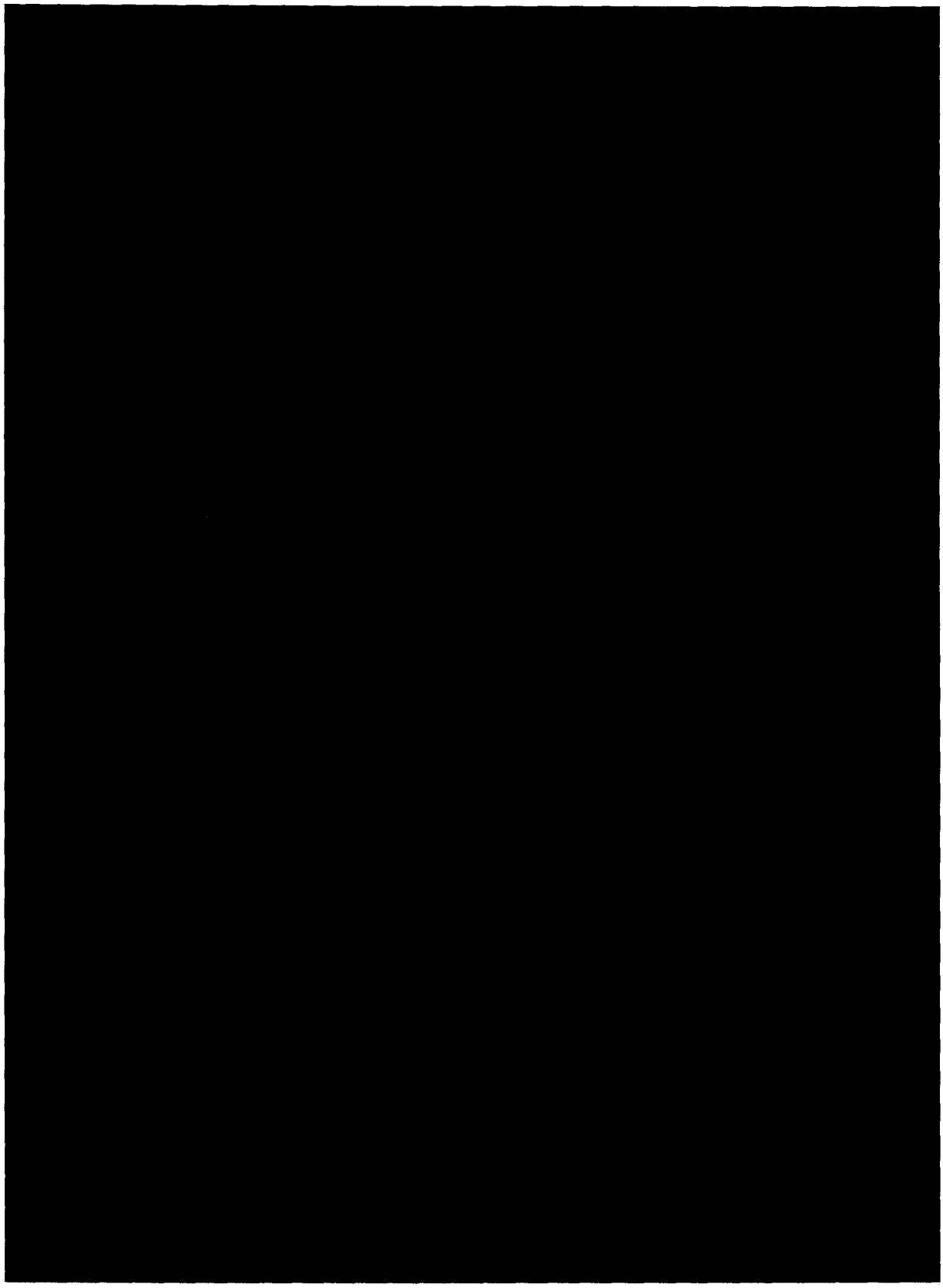
601 ± 291 (N=7) 601 (%CV=48)	1275 ± 343 (N=8) 1275 (%CV=27)	not reported

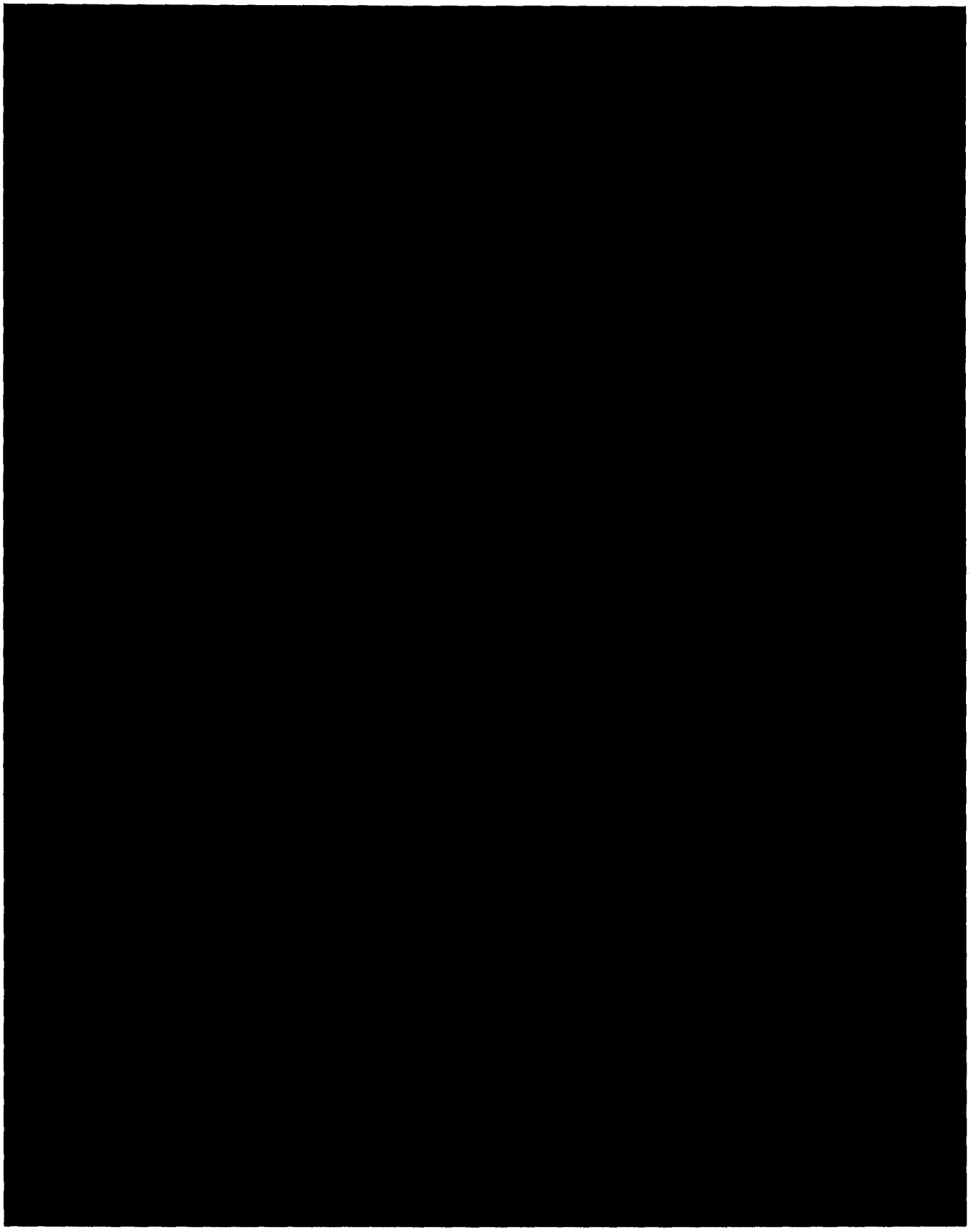
This difference of the means is very statistically significant, to p=0.0013 on a two-tailed t-test. So for the single administration, 4 mg DRSP give a higher EE concentration than 2 mg DRSP at same EE dose. Results are consistent with DRSP affecting something about EE pharmacokinetics, whether going in (bioavailability) or out (metabolism).

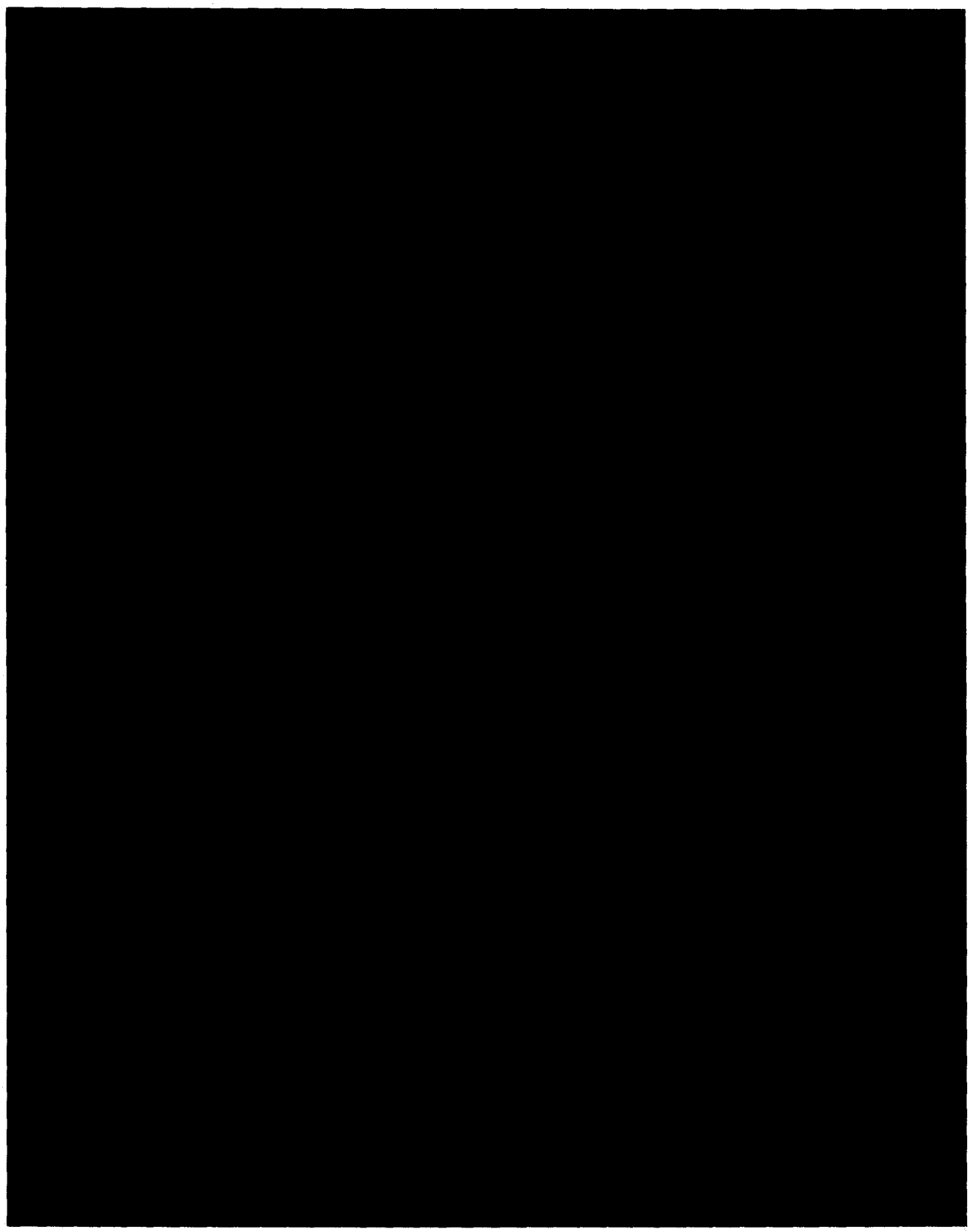
[redacted]

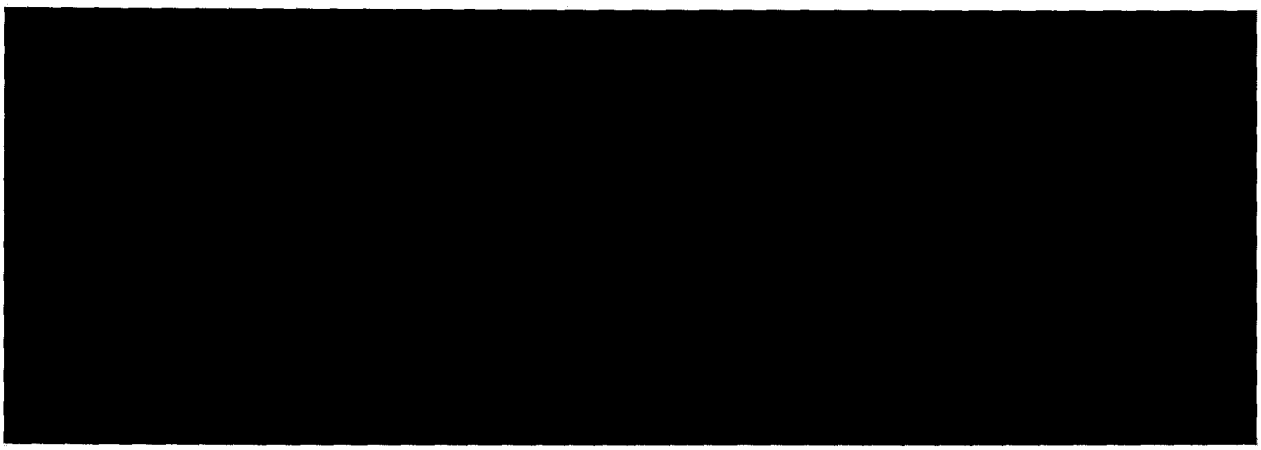












XX. Summary

208. In this report I have discussed several reasons why I am concerned about the safety of drospirenone-containing combination oral contraceptives. First, there are compelling epidemiology studies that establish a higher risk of venous thromboembolism (about two-fold) for users of DRSP-containing COCs than for users of older COCs containing a second-generation progestin (*e.g.*, levonorgestrel). The DRSP-containing COCs thus show evidence of higher risk of a serious adverse effect without evidence for any significant new benefit over older products in this class. See Section XIII above.

209. Second, it is my opinion that Bayer did not adequately study the pharmacokinetics of the other component of the DRSP-containing COCs, ethinyl estradiol. Instead they chose to rely on historical data from other preparations. Within the clinical studies I examined was evidence that DRSP could affect the PK of EE. Since VTE risk is a function of EE dose, it was a serious oversight to not test the effects of DRSP on EE bioavailability, half-life, etc. See ¶ 178-179 above.

210. Third, it is my opinion that the actual EE exposure to patients using the DRSP-containing COCs is considerably higher than indicated on the product labels for *Yasmin*® and *Yaz*®. The labels should be revised to inform potential prescribers and patients of accurate EE PK values, particularly AUC_{24}, so that they can make an informed decision about use of these products. The current US product labels also do not contain recent (2011) epidemiology results, making it difficult for a potential prescriber or patient to evaluate risks. See Sections XIII and XVIII above.

211. Fourth, because the reported patient to patient variability in EE exposure for DRSP-containing COCs is high, a significant percent of patients using them will be exposed to the high levels of EE seen with COCs containing >50 µg/d of ethinyl estradiol. COCs containing this much EE were banned by FDA in 1988. See Section XIX above.

212. Fifth, the DRSP-containing COCs induce very high levels of expression for the hepatic protein sex hormone binding globulin (SHBG). Considering the correlation between COCs that induce high SHBG expression and COCs associated with high VTE risk, the very high SHBG levels induced by DRSP-containing COCs is a significant cause for concern. See Sections X and XIX above.

XXI. Conclusion

213. Therefore, it is my opinion, to a reasonable degree of scientific certainty, that combination oral contraceptives containing drospirenone increase the risk of venous thromboembolism approximately two fold, without any therapeutic advantage, in comparison to COCs containing second-generation progestins and a comparable dose of ethinyl estradiol. Further, it is my opinion that the current product labels for drospirenone-containing COCs provide inadequate or inaccurate information concerning EE content and product risks.

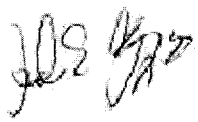
XXII. Disclosures

214. In the last four years, I have testified in deposition in the following cases related to the contraceptive patch *Ortho Evra*®: Lewis vs. Johnson & Johnson, *et al.* (2007), *Ortho Evra*® Multi-District Litigation (2008).

215. My compensation is $425/hour.

216. My *Curriculum Vitae*, listing my publications, accompanies this report as a separate document. An updated version of my CV is available on request.

Yours sincerely,



John E. Maggio, Ph.D.
van Maanen Professor of Pharmacology
and Experimental Therapeutics

Dated 1 August 2011

Appendix I. Selected Abbreviations Used

µg	microgram (10^{-6} g)
µM	micromolar (10^{-6} M or 10^{-6} mol/l)
τ	dosing interval, typically in hours
%CV	coefficient of variation (sd/mean) expressed as a percentage
[X]	concentration of X
APC	activated protein C
APCres	resistance to activated protein C
APCsr	activated protein C sensitivity ratio
AUC	area under the curve of a plot of concentration vs. time
AUC_{t1-t2}	AUC from time t1 to time t2
$AUC_{0-\infty}$	AUC from time zero extrapolated to infinity
$AUC_{0-\tau}$	AUC from time zero to time τ
AUC_{τ}	AUC from time zero to time τ
BMI	body mass index
BMJ	*Brit. Med. J.* or *British Medical Journal*
C_{avg}	average concentration
CDER	Center for Drug Evaluation and Research
C_{max}	maximum concentration
C_{min}	minimum concentration
C_{ss}	steady-state concentration
C_{∞}	concentration at time infinity
CBG	corticosteroid-binding globulin
CI	confidence interval
Cl	clearance
Cl/F	oral clearance = clearance/bioavailability
CV	coefficient of variation = sd/mean (usually as a percentage)
COC	combination oral contraceptive
CPA	cyproterone acetate
D	dose
d	day

DRSP	drospirenone
DVT	deep vein thrombosis
e	base of natural logarithms, about 2.72
E_2	17β-estradiol
EE	ethinyl estradiol
EE_2	ethinyl estradiol
e.g.	for example
EMA	European Medicines Agency (formerly EMEA)
equiv	equivalent
et al.	and others
EURAS	European Active Surveillance Study
F	oral bioavailability
FDA	US Food and Drug Administration
FI	fluctuation index
g	gram
GC	gas chromatography
GC/MS	gas chromatography coupled with mass spectrometry
GnRH	gonadotropin releasing hormone
h, hr	hour
hCG	human chorionic gonatotropin
HPLC	high performance liquid chromatography
HPO	hypothalamus pituitary ovary
hr, h	hour
i.e.	that is
IND	Investigational New Drug Application
IUD	intrauterine device
IV	intravenous
k	elimination rate constant
k_0	rate of drug delivery
kg	kilogram
l, L	liter
LAP&P	Leiden Experts on Advanced Pharmacokinetics & Pharmacodynamics

LC	liquid chromatography
LLOQ	lower limit of quantitation
LNG	levonorgestrel
ln	natural logarithm
m	meter
mg	milligram (10^{-3} g)
ml	milliliter (10^{-3} l)
M	molar or mol/l.
MAAC	Medicines Assessment Advisory Committee
MEGA	Multiple Environmental and Genetic Assessment
min	minute
MS	mass spectrometry
MSTFA	N-methyl-N-trimethylsilyl-trifluoroacetamide
NDA	New Drug Application
ng	nanogram (10^{-9} g)
nM	nanomolar (10^{-9} M or 10^{-9} mol/l)
NG	norgestrel
NGM	norgestimate
NME	new molecular entity
OBJF	objective function
OC	oral contraceptive
op. cit.	work previously cited
PE	pulmonary embolism
PEM	prescription event monitoring
PFBCl	pentafluorobenzoyl chloride
pg	picogram (10^{-12} g)
PK	pharmacokinetics
pM	picomolar (10^{-12} M or 10^{-12} mol/l)
PMDD	premenstrual dysphoric disorder
q.v.	which see
RIA	radioimmunoassay
sd	standard deviation

SH T00186D	3 mg/d DRSP + 20 µg/d EE (Studies A03328 and A41549); same doses as *Yaz*®
SH T 470 E	2 mg/d DRSP + 30 µg/d EE (Studies A470 and 9274)
SH T 470 F	3 mg/d DRSP + 30 µg/d EE (Study A470); same doses as *Yasmin*®
SH T 470 FA	3 mg/d DRSP + 30 µg/d EE (Study AI98); same doses as *Yasmin*®
SH T 470 G	4 mg/d DRSP + 30 µg/d EE (Study 9274)
SHBG	sex hormone binding globulin
$t_{½}$	terminal half-life
t_{max}	time to maximum concentration
V_d	volume of distribution
VTE	venous thromboembolism
vide infra	see below
vide supra	see above
UK	United Kingdom
US	United States
v., vs.	versus
wk	week
y	year

Appendix II. Materials Available for My Review

In addition to the original publications, textbooks, websites, and Bayer documents specifically cited above, I had access during the preparation of this report to other materials which are not specifically cited. I had access to the depositions of several Bayer employees and former employees. I had access to numerous documents from the Bayer document production which are not specifically cited here. A list of the materials available for my review accompanies this report as a separate document.

Appendix III. Timetable of Selected Events

October 1996	IND 51,693 for *Yasmin*® and contraception submitted to FDA
August 1997	IND 53,905 for *Yasmin*® and PMDD submitted to FDA (never approved)
May 1999	NDA 21,098 for *Yasmin*® submitted to FDA
August 2000	IND 60,738 for *Yaz*® and contraception submitted to FDA

May 2001	*Yasmin*® approved by FDA for contraception (approved in Europe 2000, approved in UK 2002)
May 2001	*Yasmin*® first label
November 2001	IND for *Yaz*® and PMDD submitted to FDA
April 2002	Sheldon, "Dutch GPs warned against new contraceptive pill" *Brit. Med. J.* 324: 869 (2002).
October 2002	IND 65,370 for *Yaz*® and acne submitted to FDA
February 2003	*Brit. Med. J.* "Thromboembolism associated with new contraceptive Yasmin"
July 2003	Berlex warned about misleading TV ads for *Yasmin*®
October 2003	NDA 21,676 for *Yaz*® and contraception submitted to FDA
2004-2006	Meetings with FDA to discuss concerns surrounding VTE/ATE issues throughout approval process for *Yaz*®
December 2004	NDA 21,873 for *Yaz*® and PMDD submitted to FDA
July 2005	PEM study published (online March 2005)
February 2006	Ingenix Final Study Report (later published as Seeger *et al.*, *Obstet. Gynecol.* 110: 587-593, 2007).
March 2006	*Yaz*® approved by FDA for contraception
March 2006	First *Yaz*® label
March 2006	NDA 22,045 for *Yaz*® and acne submitted to FDA
April 2006	EURAS Final Study Report
October 2006	*Yaz*® approved by FDA for PMDD
January 2007	*Yaz*® approved by FDA for acne
January 2007	*Yaz*® label change
May 2007	Dinger *et al.*, *Contraception* 75: 344-354, 2007, publishes EURAS Final Results (online in February 2007).
September 2007	Ingenix study published (Seeger *et al.*, "Risk of thromboembolism in women taking ethinylestradiol/drospirenone and other oral contraceptives", *Obstet. Gynecol.* 110: 587-593, 2007).
October 2008	Bayer warned about misleading TV ads for *Yaz*®
February 2009	Jenapharm Postmarketing Surveilance Study A32276 including adverse reactions
March 2009	Bayer warned about misleading internet links for *Yaz*®
August 2009	Lidegaard *et al.*, *Brit. Med. J.* 339: b2890, 2009 (Danish study) published online

August 2009	Bayer warned about Bergkamen facility
August 2009	van Hylckama Vlieg *et al.*, *Brit. Med. J.* 339: b2921, 2009 (MEGA study) published online.
September 2009	Leiden Report A41096 (Study Report November 2009)
March 2010	*Yaz*® and *Yasmin*® label change in Europe
April 2010	*Yaz*® and *Yasmin*® label change in US (epidemiology)
May 2010	Second Dinger article published. "Risk of venous thromboembolism and the use of dienogest- and drospirenone-containing oral contraceptives: results from a German case-control study" (Dinger *et al.*, *J. Fam. Plann. Reprod. Health Care* 36: 123-129, 2010).
March 2011	*Yasmin*® and *Yaz*® label change in US, noting that risk is highest in new users.
April 2011	Two epidemiology studies published in *BMJ*. (Parkin *et al.*, *Brit. Med. J.* 340: d2139, 2011; Jick & Hernandez, *Brit. Med. J.* 340: d2151, 2011).
May 2011	EMA announces label update regarding thromboembolism risk
May 2011	FDA Drug Safety Communication

CURRICULUM VITAE

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EDUCATION

1975	A.B. (Chemistry)	Harvard College, Cambridge, MA
1975	A.M. (Chemistry)	Harvard University, Cambridge, MA
1981	Ph.D. (Organic Chemistry)	Harvard University, Cambridge, MA

POSTDOCTORAL TRAINING

1981-1983	Postdoctoral Research Associate, University Chemical Laboratory and Medical Research Council Neurochemical Pharmacology Unit, Cambridge, UK
1984-1985	Postdoctoral Fellow, Neuropsychopharmacology Research Unit, Yale University School of Medicine, New Haven, CT

ACADEMIC APPOINTMENTS

1985-1987	Assistant Professor of Pharmacology, Harvard Medical School, Boston, MA
1987-1991	Assistant Professor of Biological Chemistry and Molecular Pharmacology, Harvard Medical School, Boston, MA
1991-1997	Associate Professor of Biological Chemistry and Molecular Pharmacology, Harvard Medical School, Boston, MA
1997-2007	Director (Chair) of the Department of Pharmacology and Cell Biophysics, University of Cincinnati College of Medicine, Cincinnati, OH
1997-	Flor van Maanen Professor of Pharmacology and Experimental Therapeutics, University of Cincinnati College of Medicine, Cincinnati, OH
2007-	Visiting Professor of Neurology, Harvard Medical School, Harvard Institutes of Medicine, Boston, MA

AWARDS and HONORS

1971-1975	Dean's List, Harvard College Scholarship for Outstanding Academic Achievement, National Merit Scholar (Harvard College, Cambridge, MA)
1975	A.B. *magna cum laude* with Highest Honors (Harvard College, Cambridge, MA)
1976-1978	National Science Foundation Graduate Fellow (Harvard University, Cambridge, MA)
1981-1982	Member of the High Table, King's College (University of Cambridge, Cambridge, UK)
1981-1982	North Atlantic Treaty Organization / National Science Foundation Postdoctoral Fellow (University Chemical Laboratory and Medical Research Council, Cambridge, UK)
1983-1984	Muscular Dystrophy Association Postdoctoral Fellow (University of Cambridge, Cambridge, UK, and Yale University School of Medicine, New Haven, CT)
1999-2002	Zenith Investigator of the National Alzheimer's Association (University of Cincinnati College of Medicine, Cincinnati, OH)
2005	President's Award of the Alzheimer's Association, Greater Cincinnati Chapter (Cincinnati, OH)

ORIGINAL PUBLICATIONS

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